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Effects of Ionizing Radiations on Mammalian Oogenesis: a Model for Chemical Effects

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A synopsis of the available data on the radiosensitivity of female germ cells is provided, the reader being referred to recent comprehensive reviews for detailed information. The effects of ionizing radiations are considered in terms of age; germ cell stage and follicular development; type, quality, and physical factors of the exposure; and criterion chosen to assess the effect (cell killing, reproductive capacity, genetic effects, etc.). A number of conclusions are drawn which might have a bearing on studies in which the effects of chemicals and drugs on mammalian species are assessed.

Ionizing radiations include those produced by the decay of radioisotopes (α, β, and γ-rays; neutrons, etc.) and those produced artificially (x-rays). The primary lesion caused by these radiations derives from an ionization—either within a cell or in the environment surrounding the cell—which may result in damage to a variety of cellular organelles (*1–4*). Radiolesions may occur within the nucleus or cytoplasm of the cell and a proportion of the changes will be repaired: however, the most important consequence of radiation damage is breakage of the chromosomes which can result in the death of the cell, or genetic changes (*5–7*).

The extensive and complex literature on the effects of ionizing radiations on the mammalian ovary has been the subject of many review articles (*3, 6–9*), and hence only the major conclusions will be restated here. It should be stressed at the outset, however, that radiation effects vary considerably between species, and indeed between strains within one species, and thus great care must be taken if results are to be extrapolated from one experimental mammal to another. Physical factors at the time of exposure have a profound effect on the response of cells to irradiation (e.g., dose rate, quality and type of radiation used, acute or fractionated exposure, hormonal status, oxygen tension, temperature). Indeed, the term "radiosensitivity" is itself meaningless unless the criterion chosen to assess the effect is carefully defined (i.e., biochemical changes, morphological effects, reproductive capacity, genetic effects) (*10*).

In the present synopsis the effects of ionizing radiations on the ovary will be described by use of examples drawn from studies involving morphology (cell killing), reproductive capacity of irradiated animals, and genetic effects. Emphasis will be placed on radiosensitivity of germ cells at different stages of mitosis and meiosis, whether within follicles or not, at different stages in the reproductive life span of the animal. For further detailed information the reader is referred to recent review articles (*6, 7*).

Effects of Irradiation during Embryonic and Fetal Life

By way of introduction, it is worthwhile to consider developmental changes which occur in unirradiated mammals.

The sole progenitors of all female germ cells are the primordial germ cells which arise outside the embryo and are first clearly identified in the wall of the yolk sac. These gonadal stem cells subsequently migrate to the developing gonadal ridges when they become oogonia. Both the primordial germ cells and

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the oogonia are capable of cell division (mitosis), and consequently their numbers greatly increase with advancing age. Once this period of intense mitotic activity is completed the oogonia undergo their last period of DNA synthesis (preleptotene stage) and subsequently embark upon the prophase of the first of two meiotic divisions. In marked contrast to the situation in the male, oocytes enter meiotic prophase during fetal life and become arrested at the diplotene stage of first prophase either by the time of, or shortly after, birth (*11*).

Primordial germ cells are highly sensitive to damage induced by ionizing radiations. For example, in embryonic rats exposed to x-rays on day 10 post coitum (pc) the population of germ cells is reduced by two-thirds within 5 days of treatment. However, the total population is subsequently partially restored to at least 50% of that in unirradiated controls owing to the mitotic proliferation of surviving primordial germ cells (*12*). It remains unclear whether the high sensitivity of the embryonic gonad is due to cell killing alone, to a reduced rate of mitosis, or to the failure of the stem cells to reach the developing gonadal ridges.

Oogonia are also highly sensitive to irradiation, their sensitivity becoming maximal when the incidence of cell division is at a peak (*12–14*). However, oogonia are not capable of restoring their original population by an increased rate of mitosis (*13*) (cf. primordial germ cells, see above). In terms of cell killing, the radiosensitivity of oogonia varies considerably between species. Essentially similar results have been obtained by exposing mice to 20-30 R and rats to 100 R x-rays (*12–14*), doses which have little (if any) affect on oogonia in the cow, rhesus monkey, or human fetuses (*7, 8*).

Oocytes at early stages of meiotic prophase become increasingly resistant to the cell killing effects of irradiation. Sensitivity decreases as the cell passes from leptotene, through zygotene (synapsis), to pachytene, but subsequently increases sharply with the onset of the diplotene stage of first meiotic prophase (*7, 15*). For example, mice exposed to 300 R x-rays on the day of birth in some strains of mice contain oocytes mainly at pachytene, which survive and pass to the diplotene/dictyate stages such that subsequent fertility is not impaired (*16*). This dose of x-rays would have had a severe effect on the population of oogonia (or oocytes at diplotene) had it been administered earlier (or later respectively) than the day of birth. However, the dose required to damage oocytes, and indeed the stage of oocyte development reached by day 1 post partum, varies considerably between inbred strains of mice (*14, 17*).

Oocytes in calf, monkey and human fetuses are far more resistant to radiation-induced cell killing than are those in mice and rats (*7*). Exposure of pregnant cows to 400 R γ-radiation has little effect on the population of germ cells during the first 119 days of intrauterine life, but exposure during the period from 119 days to 154 days pc results in a 68% reduction in the number of germ cells (*18, 19*). This highly sensitive period corresponds to a time when in controls many oocytes at pachytene and diplotene are undergoing spontaneous degeneration (atresia). Thus γ-irradiation may accelerate and increase the elimination of germ cells from the ovary (*7*).

In the fetal rhesus monkey, doses of 300-600 R x-rays have little effect on the number of oocytes within 30 days of exposure. A severe reduction in the size of the population of germ cells is achieved only after exposure to 1000 R x-rays (*20*). A similar effect is observed when human fetal ovaries maintained in organ culture are exposed to x-irradiation: a dose of 4000 R induced a 65% reduction in the population of germ cells in one ovary removed during the sixth month of gestation, as compared to the nonirradiated contralateral ovary in organ culture (*21*). By using purely histological criteria, a dose of 2000 R x-rays administered to fetal rhesus monkeys induced the same effect on the ovary as a dose of 4000 R given to fetal human ovaries (*21, 22*).

Little is known with regard to the long-term effects of irradiation administered during embryonic or fetal life. In terms of reproductive capacity, a dose of 100 R reduced the number of pups produced by mice who had been prenatally exposed to x-rays to about half the number found in unirradiated sibs (*23*). The greatest reduction in reproductive capacity occurred in animals exposed on day 13.5 pc, when most of the germ cells were oogonia. By contrast, exposure on day 16.5 pc, when the majority of germ cells are at the pachytene stage of meiosis, had only a slight effect.

Effect of Irradiation in Juvenile Mammals

In the majority of mammalian species oocytes enter the diplotene stage of meiotic prophase either before, or shortly after, birth. These oocytes are surrounded by granulosa cells such that the majority (>90%) form primordial (unilaminar) follicles. Although "waves" of follicular growth up to and including antral (Graafian) follicles occur in many mammalian species (e.g., man), ovulation does not occur until after puberty (*11, 24*).

In juvenile mice and rats, the radiosensitivity of oocytes in terms of morphological changes and cell killing increases sharply during the first few days of

life (diplotene/dictyate stages of meiosis). A dose of 20 R x-rays induces the immediate loss of some 50% of the oocytes on the day of birth in Street strain mice, whereas 86% are eliminated following treatment on the seventh day post partum (pp) (*14*). Radiosensitivity in this strain of mice is maximal on day 21 pp when only 6% of the oocytes survive a dose of 20 R; thereafter the germ cells become more resistant to irradiation, such that 12% of the population survive when exposed to x-rays during the seventh week (*7, 14*). It should be pointed out, however, that radiosensitivity varies considerably between different strains of mice: oocytes in the Bagg strain attain maximal sensitivity during the second week pp (day 14; cf. day 21 in Street mice) (*25*).

The reproductive capacity of juvenile mice broadly follows changes in the total population of oocytes, and thus varies with age. A dose of 30 R administered on day 14 pp to CF_1 mice results in sterility in 25% of the animals, while the same dose given on days 7 or 21 results in sterility in only 10% of the mice (*25, 26*). Similarly in Bagg mice, which are seemingly more resistant to x-irradiation than are CF_1 animals, only 6% become sterile after treatment with 20 R on day 14, while younger and older mice remain unaffected by the exposure (*14*).

Irradiation of the ovary also results in a shortening of the so-called fertility span. In mice of the Street strain, exposure to 20 R x-rays results in an increasing sensitivity from 40% on the day of birth to 72% on day 17 pp, after which fertility span is less affected (reduction of only 18% on day 49) (*27*). The effect in Bagg mice, which continue to produce litters for an average of about 20 weeks (*25*), is less marked than in Street or CF_1 strains of mice (6–12 weeks) (*14*).

Nothing is known as to changes in reproductive capacity following irradiation in species other than mice and rats. However, oocytes in the calf and juvenile pig are more resistant to radiation-induced cell killing than those in rodents (Table 1), and there is some circumstantial evidence to suggest that the same may be true of primates (Baker, unpublished observations). In the bovine, exposure of calves to 300–600 R γ-radiation has little effect on the number of surviving germ cells, but treatment with 900 R γ-rays eliminates half the population of oocytes within a few days (*28*). Oocytes in prepubertal pigs are slightly more radiosensitive than those in the calf: some 22% of the cells are killed by 400 R γ-radiation, while 80% are eliminated after exposure to 600 R. There is some evidence that juvenile human and rhesus monkey females may also be more radiosensitive than adults in terms of oocyte killing, although quantitative data are not yet available (*9*; Baker, unpublished observations).

Table 1. Doses of radiation required to kill all ovarian oocytes.[a]

	Radiation dose, R[b]		
	Primordial follicles		"Growing" and Graafian follicles (adult)
Species	Juvenile	Adult	
Mouse[c]	15	50	2000
	(7)	(10-15)	—
Rat[c]	100	315	4400
	—	(100)	—
Guinea pig	—	15,000	—
	—	(500)	—
Pig	—	—	—
	(500)	(>500)	—
Cow	—	—	—
	(900)	(>900)	—
Rhesus monkey	?2,000	7,000	ca. 5000
	—	(5,000)	—
Human[d]	—	?5,000	—
	—	(?2,000)	—

[a] Data from Baker (*8*). For references and time taken to eliminate germ cells see text and Baker (*8*).
[b] Figures in parenthesis are LD_{50} doses.
[c] Varies with age, strain, and radiation procedure (*7*).
[d] Depends on authority; refers to fractionated exposures to women aged under 35 years.

Radiosensitivity of Oocytes in Adult (Sexually Mature) Mammals

The ovary in adult mammals mainly consists of follicles, corpora lutea, and stroma. Of these only the follicles are sensitive to damage by ionizing radiations (*3, 7*). Only about 10% of the population of follicles are "growing" or antral (Graafian), the remainder consisting of oocytes at the diplotene stage of meiotic prophase within single layered (primordial) follicles.

It should be remembered that the mammalian oocyte remains in a prolonged period of arrested development (diplotene stage) throughout the period of follicular growth and antrum formation. It is only in the mature Graafian follicle shortly before ovulation that, in response to the LH-surge, meiosis resumes and the oocyte progresses from diplotene to the metaphase of the second meiotic division, and the oocyte is released from its follicle at ovulation (*11, 24*). The second meiotic division remains blocked at metaphase II unless the egg is penetrated by a spermatozoon.

These results from many years of research on gametogenesis have a profound bearing on the interpretation of data from experiments involving treatment with radiation or chemicals. Thus in mammals the stock of oocytes within the ovary is finite and decreases with advancing age owing to two important processes: namely ovulation and

atresia. The latter accounts for the final fate of at least 90% of all germ cells (*11, 24*). It must be concluded, therefore, that germ cells which are destroyed by chemicals or irradiation cannot be replaced, since there are no germinal stem cells in the adult mammal. Furthermore, apart from the few follicles (Graafian) which might be about to ovulate during each reproductive cycle, all of the oocytes—irrespective of their stage of follicular development—will be at the diplotene stage. It would be incorrect, however, to assume that the oocytes would therefore show uniform responses to irradiation: irrespective of the parameter chosen to assess the effect of radiation (cell death, reproductive capacity, genetic effects), radiosensitivity varies according to the stage of follicular growth and varies considerably between species (*7*).

In terms of cell killing, the primordial follicles of rats and mice are among the most radiosensitive cells known: a dose of about 300 R (rat) or 150 R (mouse) destroys all of the primordial oocytes within 18 hr of exposure (*10*). By contrast, some 26% of the oocytes which have started their growth phase and are surrounded by a single layer of cuboidal granulosa cells [stage 2 of follicular growth (*29*)] survive a dose of 4000 R x-rays, a dose which destroys all of the "growing" and Graafian follicles in this species [about 1800 R in the mouse; see Table 1 (*10, 7*)]. The reduction in the total population of germ cells is roughly equivalent when rats are exposed to 100 R and mice to 15 R (*30*), although resistant and sensitive strains of both species have been reported (*7*). It should be pointed out that the response to a given dose of x- or γ-rays varies with age (and is seemingly related to the size of the stock of oocytes), and with the duration of the post-irradiation interval before the effect is assessed. For example, several months after exposure to 31 R and 630 R the population of oocytes in rats had declined to 83% and 1%, respectively, of that in controls of the same age (*31*).

It is almost impossible to plot dose–response curves for mammalian species other than rats and mice, since they are out-bred and consequently there is a large variation in the number of oocytes per animal (and per ovary within one animal) (*32*). The only reliable information has been derived from studies in which one ovary per animal has been exposed to x- or γ-rays while the contralateral organ has been shielded to serve as control: even then the change in oocyte population can be positive or negative if the population of oocytes is not divided equally between the ovaries (*32*).

Nevertheless, such studies give an indication of the magnitude of radiation dose required to kill either half, or all, of the oocytes, and they have confirmed the observations of Reifferscheid (*32, 33*) at the turn of the century, that radiosensitivity varies considerably between species (Table 1). Thus the $LD_{50/30}$ (dose required to kill half the population of oocytes within 30 days of exposure) is about 500 R for the small primordial follicles in guinea pigs, while 15,000 R is required to kill all of the oocytes (*35*). In hamsters and rabbits a dose of 700 R destroys the majority of primordial follicles and also a proportion of the larger follicles (*3, 36, 37*). By contrast, oocytes in rhesus monkeys are highly resistant to cell killing by x- or γ-rays, the $LD_{50/30}$ dose for primordial follicles being 5000 R, a dose which also destroys all of the "growing" and Graafian follicles (*7, 32*). Very much higher doses are required to destroy all of the oocytes (7,000 to 12,000 R, depending upon the post-irradiation interval chosen to assess the effect) and the animals continue to produce offspring. There is some evidence that oocytes in young women may show comparable radiosensitivity to those in the rhesus monkey, although those in women over 40 years old are rapidly depleted by x- or γ-rays (*9*).

Once the LH-surge has induced the resumption of meiosis in oocytes within Graafian follicles, radiosensitivity of the oocyte increases sharply. Such oocytes generally are capable of being fertilized and sustaining early embryonic development but they subsequently die either shortly before, or immediately after, implantation (so-called "dominant lethals") (*6, 7*). By these criteria, which are often considered under the general heading of genetic effects, oocytes at metaphase I are ten times more radiosensitive than those at the diplotene stage (*38*).

In terms of changes in reproductive capacity, exposure to ionizing radiations induces sterility when the available oocytes have been eliminated. It should be remembered, however, that most female mammals cease to reproduce many weeks, months, or even years (e.g., human female) before the median age at death. Care must therefore be taken to ensure that animals are randomly assigned to treated and control groups, which are then maintained under identical conditions if the change in age at reproductive senescence is to be accurately determined. Such animals, whether irradiated or not, generally show an absence of estrous cycles once follicles and corpora lutea are no longer present in the ovary (*3, 7*). However, the situation in mice and rats is complicated by the fact that more or less normal cycles, or periods of constant estrus, can continue for prolonged periods after exposure to doses of up to 4000 R, a dose known to eliminate all of the population of follicles. It is generally accepted that most of the estrogen produced by the

ovary is derived from the pre-ovulatory follicles, but in these irradiated rodents estrogen secretion must continue from an extrafollicular source (*3, 7, 39*).

Other measures of reproductive capacity in rodents include fertility span (interval between first and last litters), which is reduced proportional to the dose administered, and the size of litters. Both the overall number of litters produced by irradiated females, and the number of young per litter are reduced by exposure to radiation (*3, 7*).

In contrast to the situation in rodents, rhesus monkeys continue to experience normal menstrual cycles for many months after exposure to doses of up to 4000 R x-rays, although the cycles are eliminated by higher doses. Once again these results could be predicted on the basis of changes in the population of germ cells which survive the radiation exposure (*32, 40*). Irradiated rhesus monkeys continue to produce viable young after exposures of up to 2000 R, although higher doses seemingly result in resorption or stillbirths (*7, 40*). The incidence of abortion is greatly increased if the irradiation reaches the gut, uterus, and other abdominal organs, compared to a low rate of still births when the radiation exposure is localized to the ovaries (*7*).

While ionizing radiations generally induce sterility, or at least reduced fertility, there is a paradoxical effect in which low doses of x-rays are used to improve fertility. These low doses induce superovulation in rats and mice (*41–43*), and the effect may be similar to the now discredited practice of ovulation induction with x-rays in women (*44, 45*).

The genetic effects of exposure to ionizing radiations are highly complex and are difficult to summarize here: however, they have been extensively reviewed elsewhere (*6, 7, 46*). The unbalanced products of translocations usually result in dominant lethals which are scored as pre- or post-implantation deaths of the embryo (see above). The frequency of dominant lethals varies between species, and with the stage of development of the oocyte; mature oocytes at diplotene in hamsters and guinea pigs are more sensitive to the induction of dominant lethals than are those in mice (*47*).

Ionizing radiations also cause the elimination of whole chromosomes from germ cells. The loss of an autosome is probably lethal owing to the loss of many genes, but the loss of a Y chromosome, or of one of a pair of X chromosomes, may not have an appreciable effect. Thus mice which are deficient in a sex chromosome (XO) are fertile (*48*), although XO humans (Turner's syndrome) are sterile and only have streak ovaries. Russell (*48*) found 21 X chromosome deletions among 6674 female progeny derived from oocytes (at diplotene) irradiated in multilayered follicles. The effect seemed to be inversely proportional to dose rate, the incidence being 0.31% when mice were exposed to 400 R x-rays at 80 R/min, 0.66% when the 400 R was given as γ-rays at 0.6 R/min, compared with a spontaneous incidence in controls of 0.05% (*48, 49*).

Another effect of irradiation is the induction of mutations. The incidence of point mutations is lower following exposure to fractionated doses of radiation than when the dose is given acutely (*6*). Thus the mutation rate in mice treated with an acute dose of 50 R is only one-third of that with a single exposure to 400 R. However, when the 400 R was given as eight fractions of 50 R, only half the mutations were obtained as with the acute exposure to 400 R (*6*). Mutation induction is also dependent upon the type of irradiation: exposure to fast neutrons is 20 times as effective than γ-radiation exposure (*50*). The mutation rate in mouse dictyate oocytes subjected to neutron irradiation has been estimated to be 0.3×10^{-7} per locus per rad, but for γ-rays the incidence of mutations is not significantly different to that in control (nonirradiated) oocytes (*6, 50*).

There is certainly no "safe" dose below which mutations will not be induced, although the observed frequency of this form of genetic damage is much lower than previously anticipated (*6*). Russell (*51*) has found only three specific locus mutations among 258,400 progeny of mice exposed to 412 R chronic γ-radiation. An analysis of this data reveals that oocytes within primordial follicles are the most resistant to mutation induction (which is in marked contrast to cell killing effects; see above), no mutations being scored in 71,324 offspring conceived more than 7 weeks after treatment. By contrast, those oocytes which were probably in "growing" follicles at the time of exposure produced 11 mutations out of a total of 169,325 offspring (*6*).

A prerequisite for genetic studies is the availability of inbred strains, and thus of specific genetic markers, to detect mutations and chromosomal breaks. It is not surprising, therefore, that the vast majority of genetic studies on the effects of ionizing radiations in mammals have been carried out in mice. Only tentative conclusions can be drawn as to the applicability of these results to man, based on the results of analyses of nuclear detonations and accidents. These results certainly show that the incidence of stillbirths, congenital malformations, leukemia, etc. are increased after radiation exposure, but the investigations were designed to detect only dominant genetic traits which have so far not been detected (*6, 7, 52*).

It is most unlikely that further information on the

genetic effects of ionizing radiation in primates will be forthcoming, and thus the value of estimates of the so-called "doubling doses" (those which double the incidence of mutations found in controls) should be questioned. Dahl-Iversen and Hamburger (*52*), using data derived from mice, suggested that the dose of radiation required to double the frequency of mutations is of the order of 30 to 80 R, but Neel (*53*) believes that this estimate should be revised upwards (*54*).

Conclusions

It remains unclear, at least to the author, whether studies involving ionizing radiations are a suitable model for chemical effects, apart of course from the radiomimetic drugs. Nevertheless there are some rather obvious pitfalls that need to be considered.

Results must only be interpreted in terms of the specified criterion chosen to assess the effect (cell killing; reproductive capacity; genetic effects; etc.). In some cases germ cells may be readily killed by exposure to radiation (e.g., oocytes at diplotene in mouse primordial follicles), but viable progeny can be derived from the surviving cells, and these may show relatively few chromosomal aberrations and virtually no mutations.

Control and treated animals in repeat experiments must be treated under identical environmental conditions, and the dose, type, quality and fractionation must be the same in duplicate experiments if valid comparisons are to be made.

Extrapolation of the results of experiments in one species to another, even a closely related species (e.g., mouse versus rat; cow versus pig; monkey versus human) is a hazardous procedure and may not be justified.

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